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Activating RNA, mastering disease

Systemic administration of a novel development candidate, MTL-CEBPA, upregulates the liver-enriched transcription factor C/EBP-α and reverses CCl4-induced liver failure in vivo

Reebye V[1], Voutila J[2], Huang K3,4, Muragundla A[5], Jayaprakash A[5], Vadnal P[5], Huber H[6], Habib R[2], Saetrom P[7,8], Rossi J[9], Habib N[1]*

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MTL-CEBPA upregulates C/EBP-α by transcriptional activation

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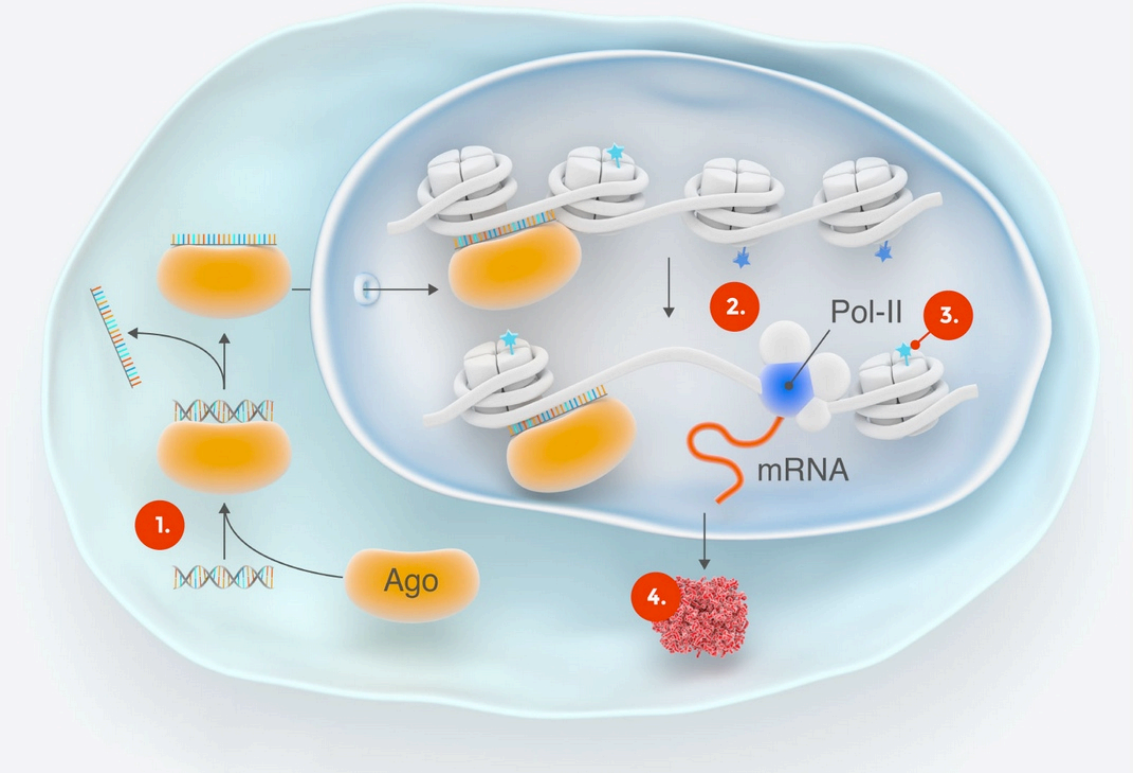

1. Loading of saRNAs into Ago2 protein
2. saRNA-Ago2 recruit transcription complexes
3. Promoter remodelling
4. Long lasting protein up-regulation

C/EBP-α is an attractive target in liver disease

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C/EBP-α transcription factor

- Master regulator
  - cell lineage determination
  - cell growth and proliferation
  - maintaince of metabolic balance and body weight homeostasis
- Essential role in hepatocytes
  - differentiation
  - lipid and glucose homeostasis

Rationale for upregulation in liver disease

- Dysregulated in major liver diseases, including NAFLD, NASH, and HCC
- Overexpression reduced fibrosis in mice
- Up-regulating improved liver function in DEN model of cirrhosis and HCC in rats

Mei et al. Hepatology Research 2007; 37: 531–539 | Tao et al. Apoptosis (2012) 17:492–502 | Reebye et al. Heptaology 2014;59:216-227

MTL-CEBPA dosed in CCl4 model of liver failure

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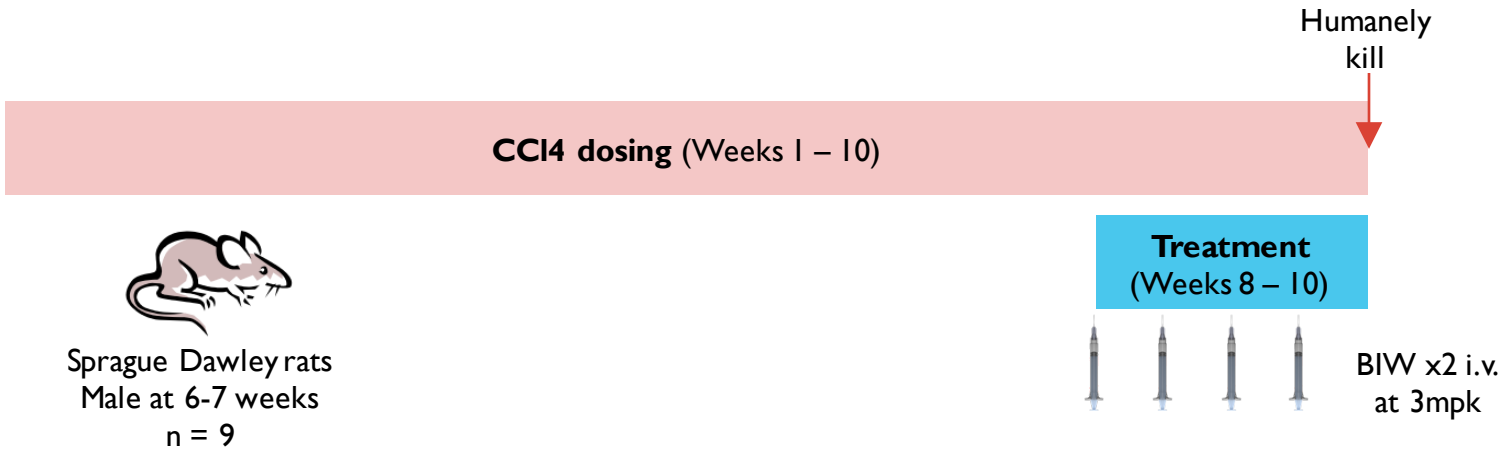
- ✅ Hepatic fatty infiltration
- ✅ Fibrosis
- ✅ Liver injury
- ✅ Impaired liver function



MTL-CEBPA restores CEBPA mRNA in cirrhotic liver

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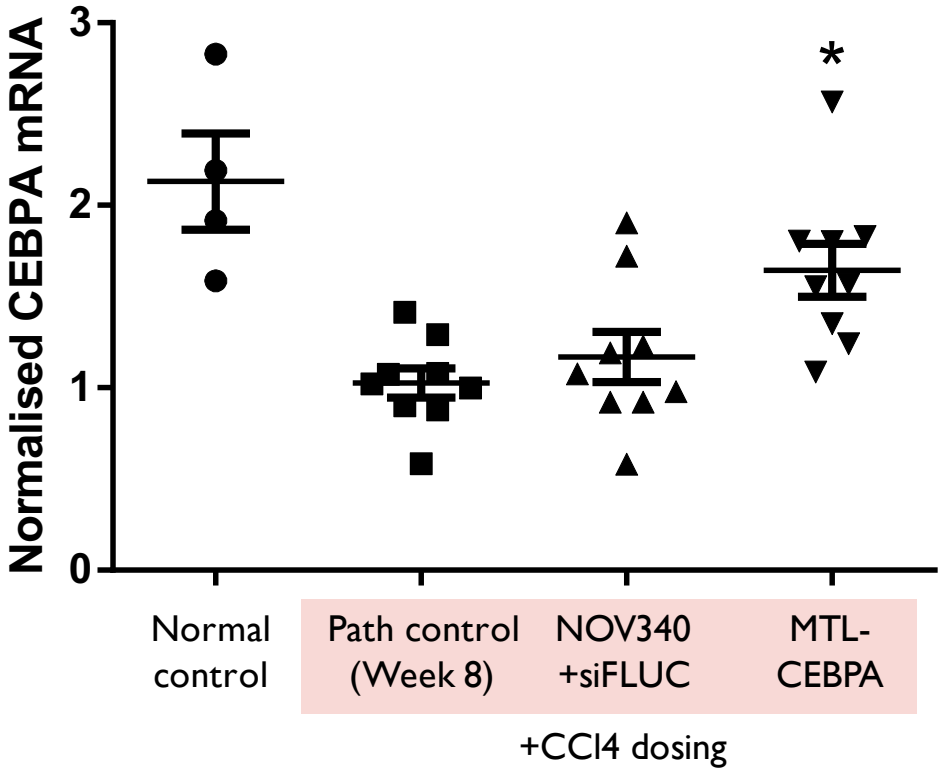

MTL-CEBPA normalises liver hydroxyproline

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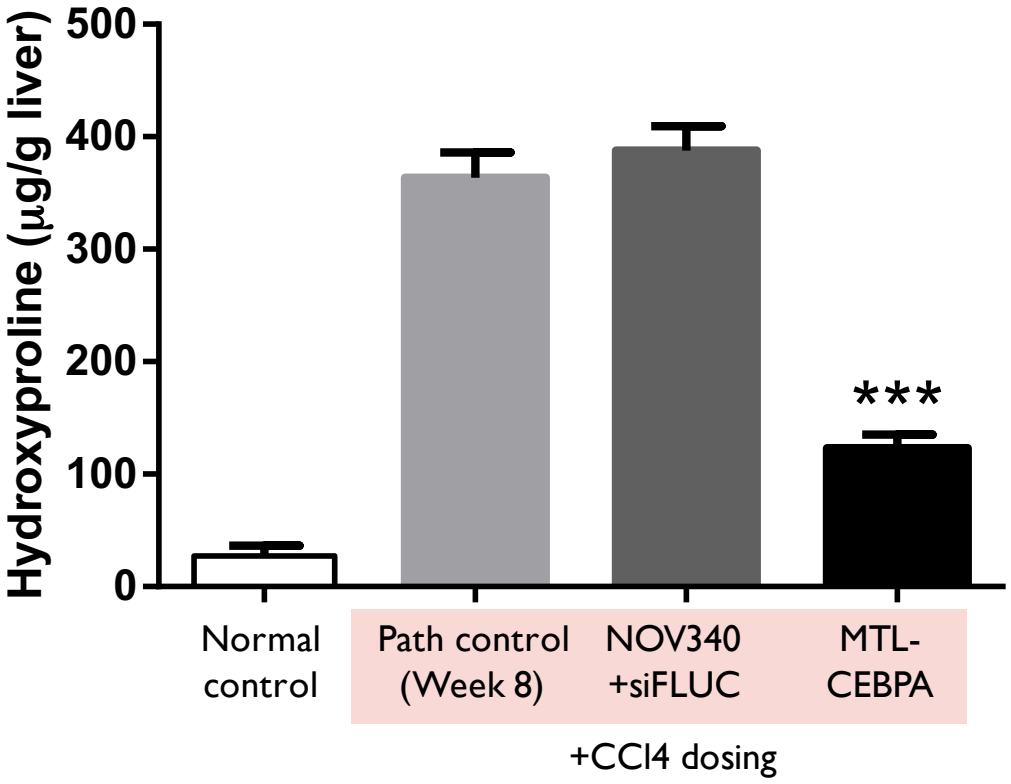

Reduced fibrosis and fatty infiltration in MTL-CEBPA treated animals at week 10

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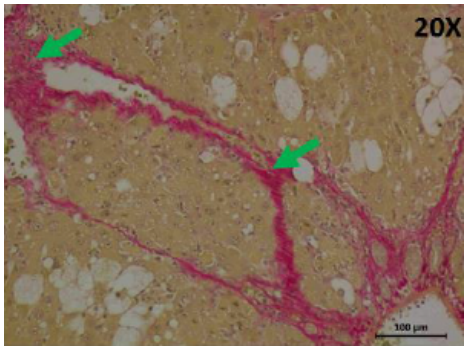
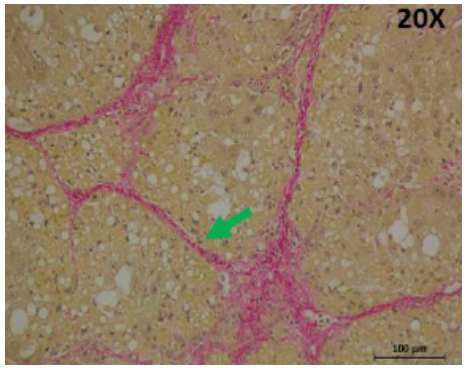
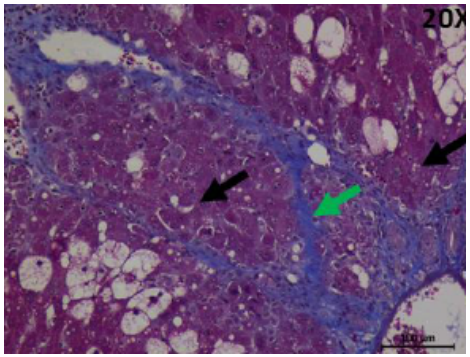
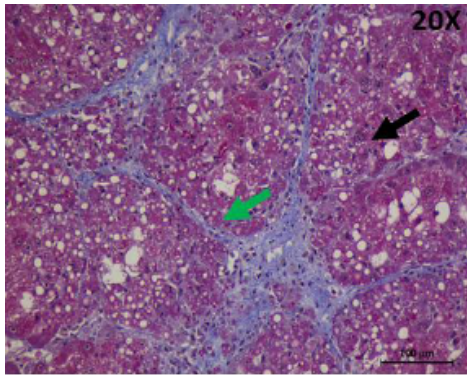
NOV340 + siFLUC	MTL-CEBPA
	
	

MTL-CEBPA normalises serum bilirubin

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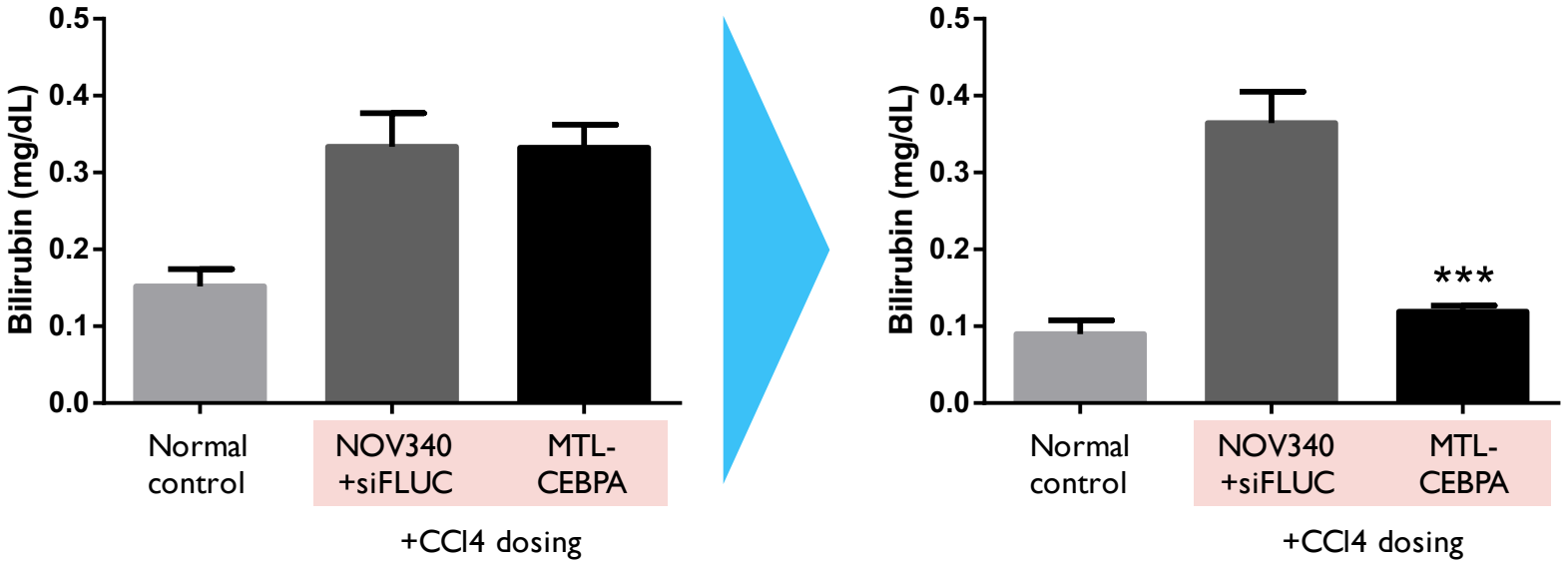
Pre treatment
Week 8

Post treatment
Week 10



MTL-CEBPA normalises serum albumin

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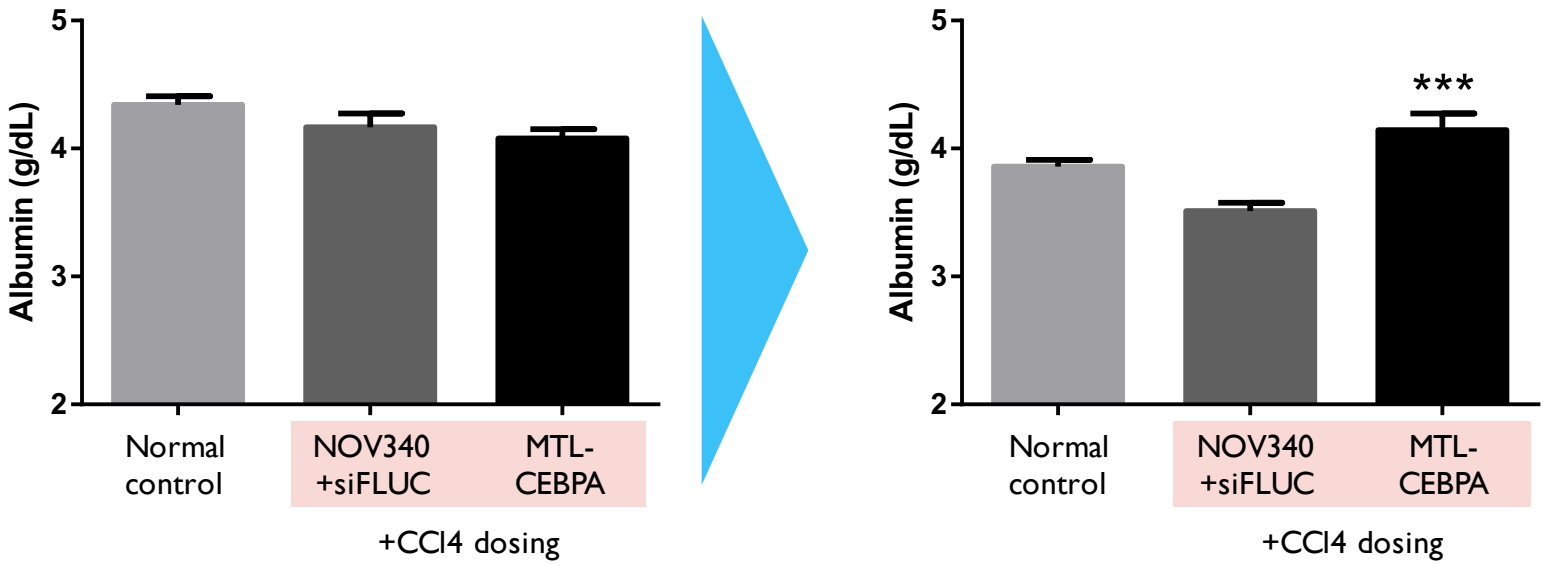
Pre treatment
Week 8

Post treatment
Week 10



MTL-CEBPA normalises prothrombin time

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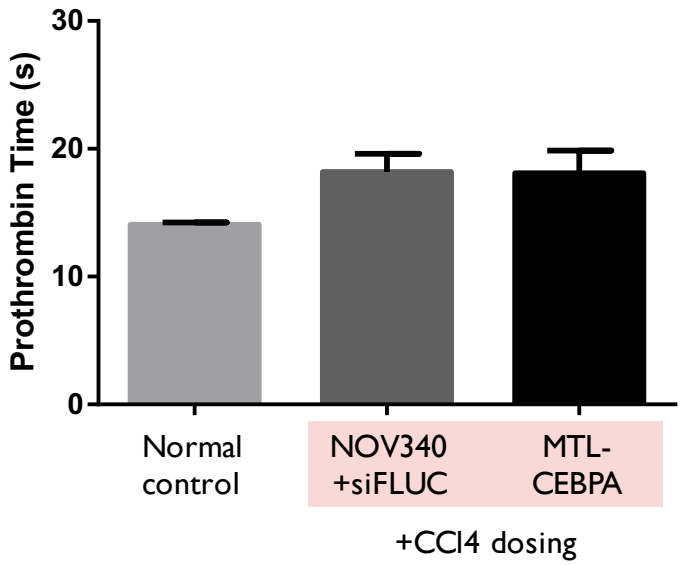
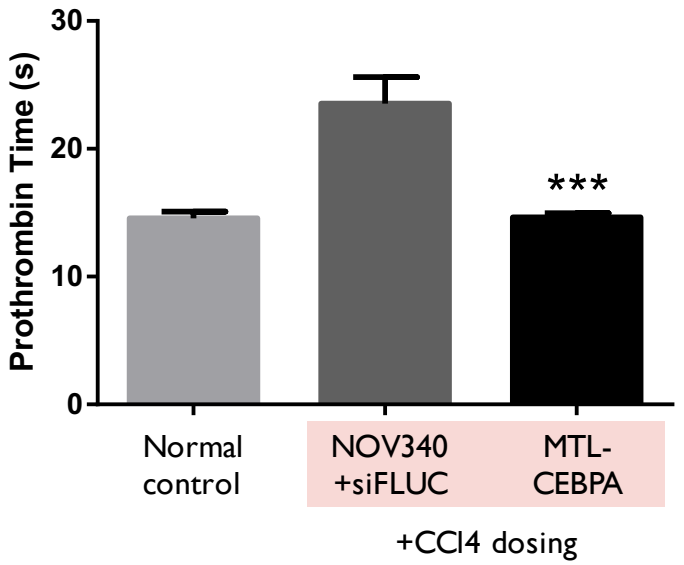
Pre treatment
Week 8



Post treatment
Week 10



MTL-CEBPA attenuates hyper-ammonaemia

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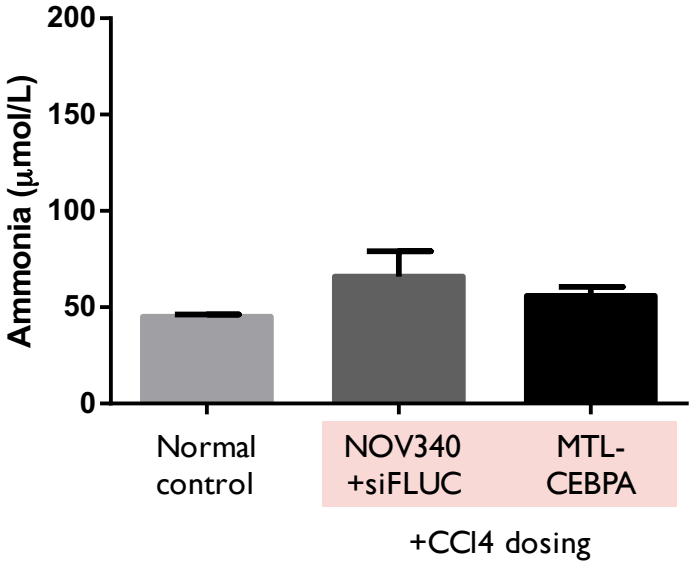
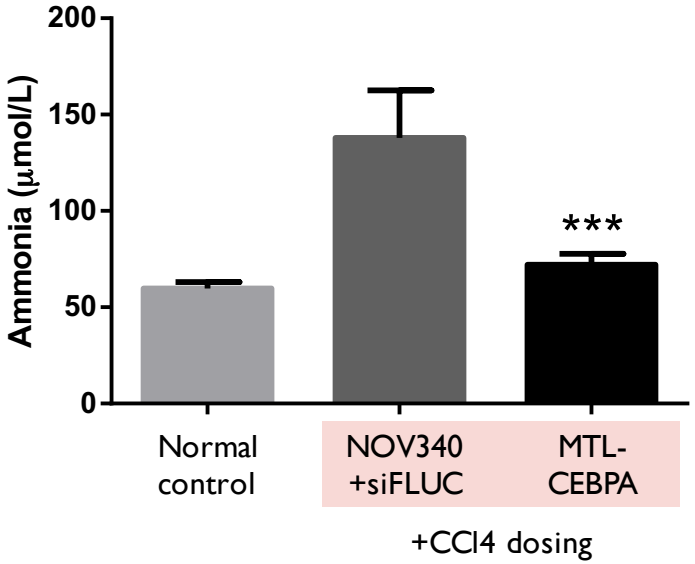
Pre treatment
Week 8



Post treatment
Week 10



MTL-CEBPA normalises serum AST

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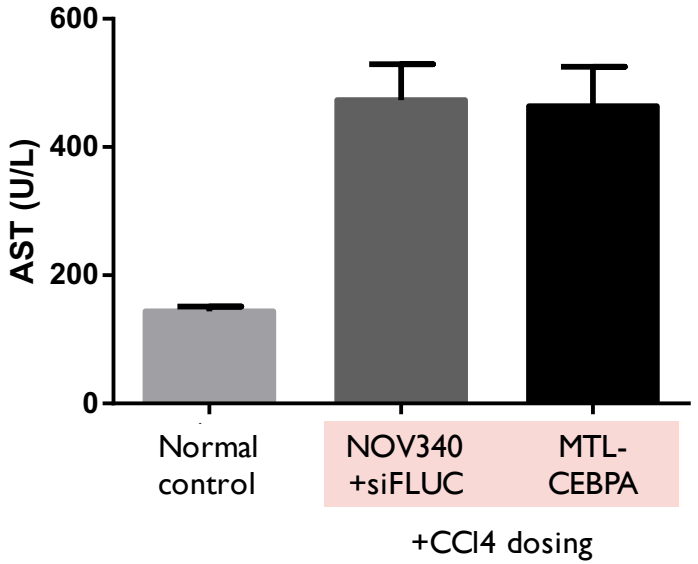
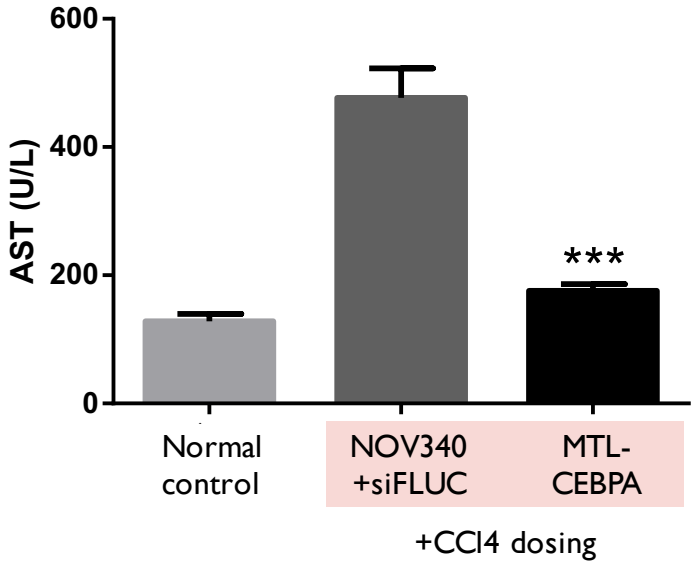
Pre treatment
Week 8



Post treatment
Week 10



MTL-CEBPA normalises serum ALT

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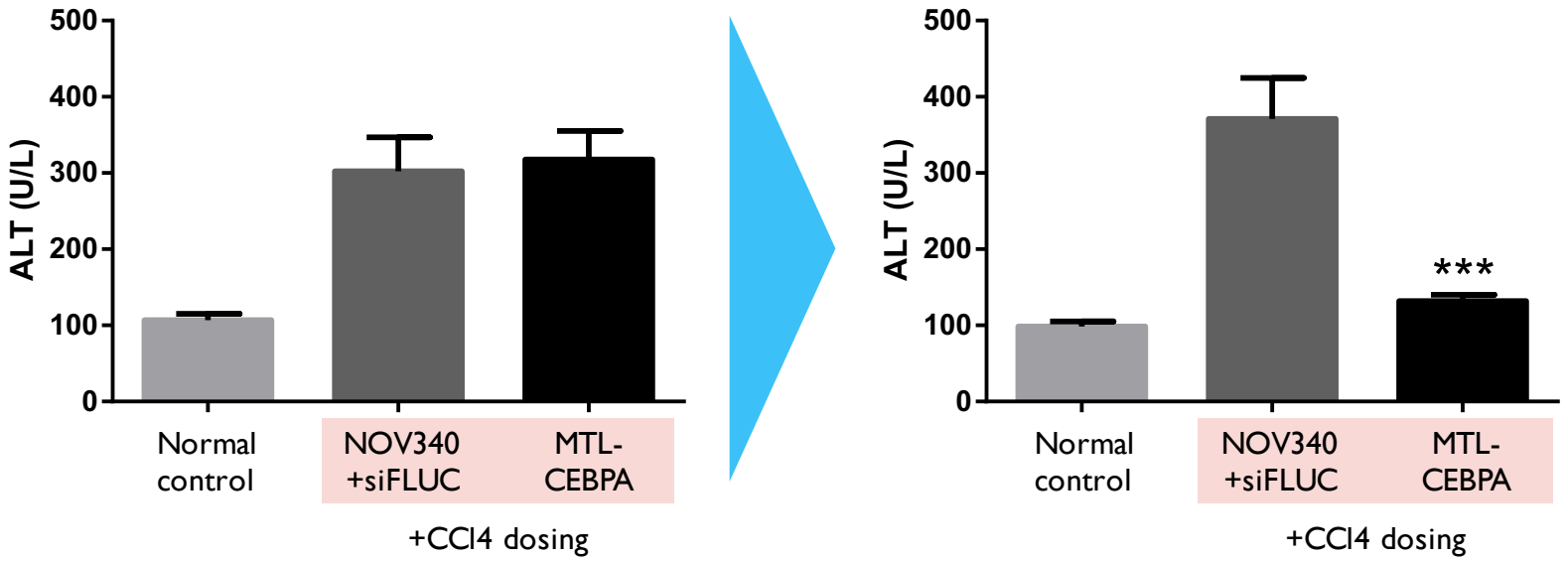
Pre treatment
Week 8

Post treatment
Week 10



MTL-CEBPA normalises serum ALP

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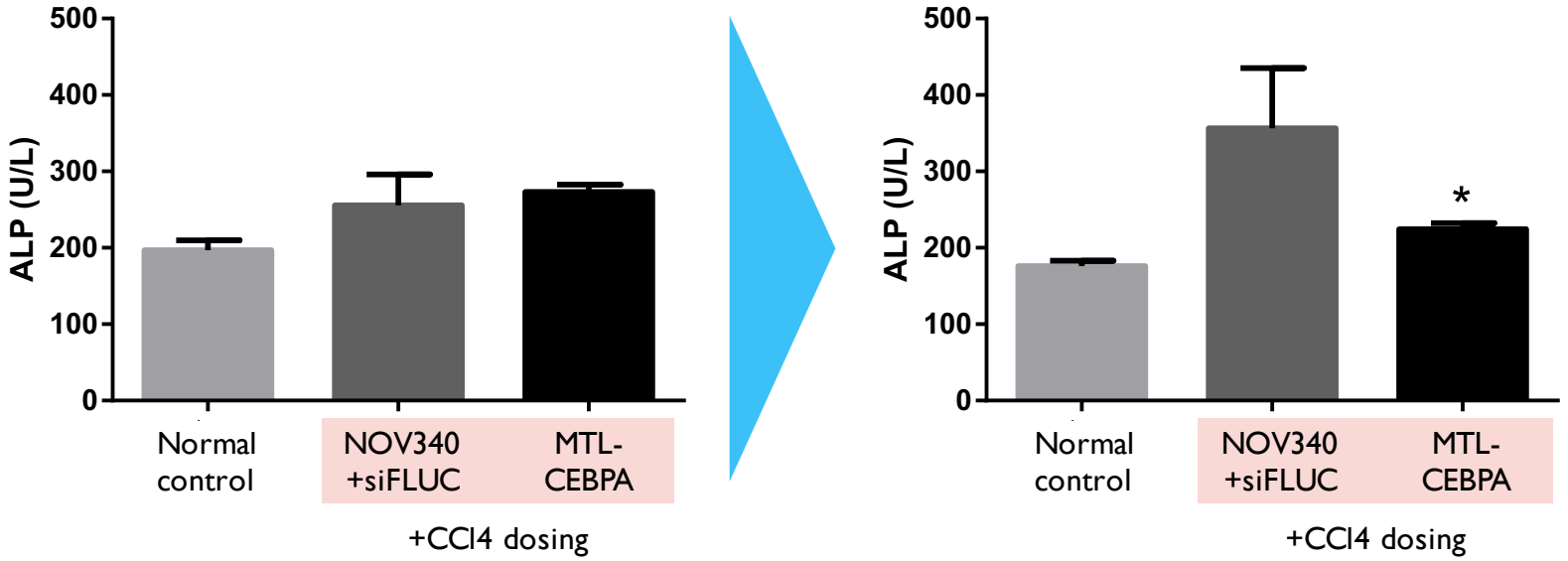
Pre treatment
Week 8

Post treatment
Week 10



MTL-CEBPA normalises body weight

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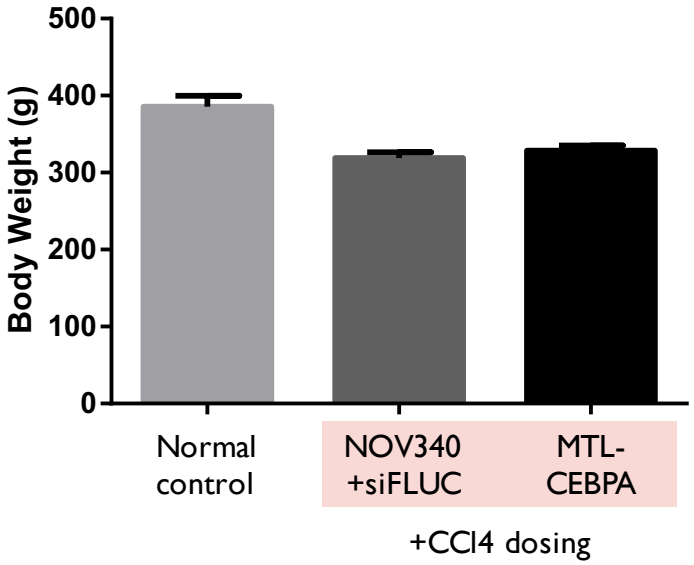
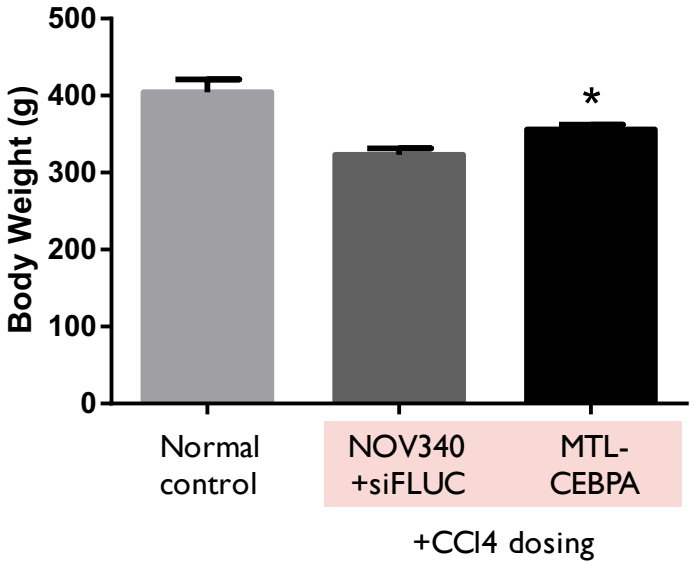
Pre treatment
Week 8



Post treatment
Week 10



Clinical track record of MTL-CEBPA liposomal formulation SMARTICLES

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MRX34

- Well tolerated at 110 mg/m2 in ongoing Phase I study in liver cancer and hematological malignancies
- 9 mg/kg NOAEL identified in NHP toxicology study
- Tumour regression in mouse model of HCC at 0.3 mg/kg

PNT2258

- Anti-tumour activity at 120 mg/m2 in Phase II in non-Hodgkin's Lymphoma
- Well tolerated in Phase I up to 150 mg/m2

OUTReACH
Phase 1 in HCC with impaired liver function

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First patient in	▪ Q1 2016
Design	▪ Open label, First in Human dose escalation in cohorts of 3 patients
Indications	▪ Advanced tumour diseases with low serum albumin levels, characterised by primary or secondary liver tumours
Objectives	▪ Primary: To determine the safety of administering MTL-CEBPA to patients with liver tumours and low serum albumin ▪ Secondary: To determine the RP2D; characterise the PK of MTL-CEBPA; characterise the PD of MTL-CEBPA; to increase serum albumin and/or decrease serum bilirubin
Administration	▪ 60min I.V. infusion ▪ QWx3 + 1 week rest (4 week cycle)
UK centres	KING'S College LONDON; Imperial College London; UCL; Newcastle University; University of Liverpool; University of Cambridge

Conclusion

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- MiNA Therapeutics developing short activating RNA compounds to selectively up-regulate gene expression
- MTL-CEBPA candidate targets CEBPA gene promoter for increased C/EBP-α expression
- MTL-CEBPA reverses CCl4 induced liver failure *in vivo*
- ***OUTREACH*** Phase I study initiating in Q1 2016